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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/448,420	11/22/1999	MICHAEL SEUL	42970-3	5017

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EXAMINER

PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 10/07/2003

31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/448,420

Applicant(s)
Seul et al

Examiner
Padmashri Ponnaluri

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jul 21, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 129-174 is/are pending in the application.
- 4a) Of the above, claim(s) 152, 153, and 167 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 129-151, 154-166, and 168-174 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other: _____

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DETAILED ACTION

1. The response filed on 7/21/03 has been fully considered and entered into the application.
2. The amendment H, filed on 3/24/03 and amendment G filed on 12/02/02, and the amendment F filed on 10/15/02 have been entered into the application.
3. New claims 164-174 have been added by the amendment G, and claims 160-163 have been added by the amendment F filed on 10/15/02.
4. Claims 129-174 are currently pending in this application.
5. Claims 152-153 are withdrawn from further consideration by the examiner, 37 CAR 1.142(b) as being drawn to a non-elected species election. Election was made **without** traverse in Paper No. 10. New Claim 167 has been withdrawn as drawn to non-elected subject matter (peptides).
6. Claims 129-151 and 154-166, 168-174 are currently being examined in this application.
7. The rejections of claims 129-151, 154-159 under 35 U. S. C. . 112, second paragraph have been withdrawn in view of applicants amendments to the claims.
8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
9. The rejection of claims 129-138, 142-146, 151, 154 and 159, and new claims 160-166, 168-174 under 35 U.S.C. 102(b) as being anticipated by WO 93/06121 (Dower et al) is maintained for the reasons of record set forth in the previous office action mailed on 4/9/02.

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10. The rejection of claims 129-138, 142-146, 151, 155-159 and new claims 160-166, 168-174 under 35 U.S.C. 102(e) as being anticipated by US Patent 5,968,736 (Still et al) is maintained for the reasons of record set forth in the previous office action mailed on 4/9/02 .

11. The rejection of claims 129-159, and new claims 160-166, 168-174, under 35 U.S.C. 103(a) as being unpatentable over Dower (WO 93/06121) in view of Metzeker et al (US patent 5,728,529) is maintained for the reasons of record set forth in the previous office action mailed on 4/9/02.

New Rejections Necessitated by the Amendment

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 129-151, 160-166, 168-174 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyce et al (J. Am. Chem. Soc., Vol. 116, No. 17, 1994).

The instant claims briefly recite a method of identifying a compound of interest in a library of compounds, each of said compounds being bound to a solid support, and prepared by split synthesis, adding one or more tags to the solid support; and decoding the code composed of one or more tags; performing an assay capable of indicating that any compound in the library has a property of interest; decoding the code composed of one or more tags to identify the compound,

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wherein the decoding step is carried out without isolating the solid support comprising the compound from other solid support and without detaching the tag from the solid support, and wherein the decoding step comprises in situ optical interrogation of the tag.

Boyce et al disclose peptido steroidal receptors for opioid peptides. The reference discloses split synthesis using polystyrene beads. The reference discloses that the combinatorial synthesis led to 10^2 variants of V1 and was encoded with eight molecular tags using a binary tagging method. Finally encoded split synthesis was employed with eight more tags to complete V2. This double split synthesis led to a 10^4 member library in which each different member of the library was attached to a different synthesis bead (refers to steps a)-e) of the instant claims). The reference discloses to test the library for receptor substrate binding. The binding screen was conducted as a solid phase assay in which a sample of the beads were treated with a dilute solution of substrate tethered to an intensely colored dye. The dye-linked receptor library was then screened for binding with encephalon (refers to the instant claim step f)). The reference discloses that many beads had developed light orange coloration and few turned bright red (refers to said decoding step comprises in-situ optical interrogation of the instant claims). The reference discloses that bright red beads (refers to other solid supports) and decoded their synthetic history. Thus, the reference clearly anticipates the claimed invention.

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Response to Arguments

14. Applicant's arguments regarding the rejection of claims over DOWER et al filed on 10/15/02 have been fully considered but they are not persuasive.

Claims 129-138, 142-146, 151, 154 and 159 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/06121 (Dower et al).

Dower et al disclose a general stochastic method for synthesizing random oligomer which can be used to synthesize compounds to screen for desired properties. The reference discloses that the use of the identification tags on the oligomer facilitate identification of oligomer with desired properties (see the abstract). The reference discloses that the random oligomer are synthesized on solid supports, or particles, but may be cleaved from these supports to provide a soluble library. The oligomer are composed of a sequence of monomers, and the library is screened to isolate individual oligomer that bind to a receptor, or possess a desired property (see page 4). The reference discloses that an identifier tag is used to identify the sequence of monomers in the oligomer. The reference discloses that the identifier tag is directly attached to the oligomer with or without an accompanying particle, to the solid support upon which the oligomer is synthesized (see page 4). The reference discloses that the identifier tag may be composed of a set of light addressable compounds, such as fluorescent or phosphorescent compounds, which are incorporated into the beads or particles on which the oligomer of the oligomer library are synthesized. The reference discloses that the coded identifier tags may be used so that each monomer is assigned a specific binary number (i.e., see page 26, lines 3-4) (refers to bits of binary code of the instant claims). The reference discloses such compounds are well known in the art (i.e., see last paragraph in page 4 bridging page 5). The reference discloses a method for producing tagged synthetic oligomer libraries (i.e., see pages 15-19). The reference discloses split-pool synthesis of the oligomer library (i.e., see page 16). The reference discloses the method for identification of the sequence of the oligomer (i.e., page 19). The reference discloses that the tags may be attached immediately before, during, or after the monomer addition, as convenient as compatible with the type of identifier tag, modes of attachment and chemistry of oligomer synthesis. The identifier tag is

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added when the solid support that have undergone a specific monomer addition step are physically together so can be tagged as a group. The reference discloses that the fluorescent beads are recovered from the positive wells. The beads are removed and sorted by FACS. The reference discloses that the compounds of the library are identified using a competitive assay, in which diminished fluorescence caused by the oligomer library competing with the ligand are identified (i.e., see page 31). The reference clearly anticipates the claimed invention.

Applicants argue that the positive beads are isolated by affinity adsorption. Applicants argue that the Dower uses oligonucleotide tags, which is not an optical tag and is not optically decoded. Applicants arguments have been considered and are not persuasive, since Dower et al teach that the identifier tag may be composed of a set of light addressable compounds, such as fluorescent or phosphorescent compounds, which are incorporated into the beads or particles on which the oligomer of the oligomer library are synthesized.

Further applicants argue that Dower teaches that the light addressable fluorescent beads are isolated prior to the tag identification. This is contrary to the claimed invention, which provided in situ optical interrogation of beads without isolation from other beads in the array. Applicants arguments have been considered and are not persuasive, because in the instant claimed method of identifying a compound which is attached to a bead from a mixture or pool of beads by in-situ optical interrogation. However, applicants arguments seem to be stating that the instant claim recites in-situ optical interrogation of the compound attached to the bead to determine the structure of the compound attached to the bead, which is not present in the instant claim. In response to applicant's argument that the references fail to show certain features of

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applicant's invention, it is noted that the features upon which applicant relies (i.e., determining the sequence or the structure of the compound attached to the bead by in-situ optical interrogation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicants arguments are not persuasive, since Dower et al teach after the receptor assay the positive beads are identified by the visual inspection of the fluorescent beads which refers to the '... decoding the code composed of tag to identify the compound associated with the code, ...wherein the decoding step comprises in-situ optical interrogation of the tag' of the instant claims. The new claims 160-166, and 168-174 have been included in this rejection because the rejections of record teach all the limitations. Thus the reference clearly anticipates the claimed invention.

15. Applicant's arguments filed on 10/15/02, regarding the rejection of claims over Still et al (US Patent 5,968,736) have been fully considered but they are not persuasive. .

Claims 129-138, , 142-146, 151, 155-159 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,968,736 (Still et al) .

Still et al disclose methods for recording the reaction history of a solid support. The reference discloses encoded combinatorial chemistry, in which sequential synthetic schemes are recorded using organic molecules, which define choice of reactant, and stage, as the same or different bit of information. The reference discloses that various products can be produced in multistage synthesis, such as oligomer and synthetic non-repetitive organic molecules (see abstract). The reference discloses that nested families of compounds can be employed as identifiers, where the number

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and/or position of a substituent define the choice, and alternatively detectable functionalities such as radioisotopes, fluorescers, halogens can be used (see abstract). The reference discloses that the invention provides methods and compositions for encoded combinatorial synthesis whereby at each stage of the synthesis one or more identifiers are provided which encode and event associated with a particle stage in the synthesis of the compound on the support (i.e., see column 7, lines 1-4). The reference discloses that the N identifiers, and M distinguishable states are provided (see column 7, lines 14-15); and in case if M is 2 where the two states could be the presence of absence of identifier, the synthesis thus defined by a base 2 or binary code (i.e., see column 7, lines 15-18) (refers to the fluorophore tag represents a bit of binary code of the instant claims). The reference discloses that the synthesis of oligomer on solid support begin with a number of beads, which would be divided into groups, and then add the reagents and the identifiers which encode the reagent and the stage of the reaction. And after the synthesis is completed, the compounds are screened for desired property either after detachment of the ligand (compound) from the bead or **while still attached** (i.e., see column 17, lines 4-6). The reference discloses that the beads with ligand attached are incubated in aqueous buffer with monoclonal antibody (for the property to be tested), and the fluorescent beads with attached monoclonal antibody are identified and separated by manually or using FACS from the unstained beads, so long as the tags are retained on the bead under the conditions of sorting. The reference teaches that the fluorescent beads with attached compound are identified from the unstained beads, thus, the reference analyzed the fluorescent data of the beads, to identify the compound of interest in the library. Thus, the reference clearly anticipates the claimed invention.

Applicants argue that Still does not anticipate Applicants' invention, because nowhere does Still teach or suggest tag decoding without isolating the solid support of interest from other solid supports. In fact, Still requires separation of beads containing attached fluorescent-Mab by means of FACS.

Applicants arguments have been considered and are not persuasive because the Still et al teach that families of compounds can be employed as identifiers, where the number and/or

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position of a substituent define the choice, and alternatively detectable functionalities such as radioisotopes, fluorescers, halogens can be used. And the reference after synthesis is completed, the reaction products are screened for desired property by incubating the beads with fluorescently labeled Antibody and the positive beads are identified and separated, which refers to the in-situ optical interrogation of the beads to identify the compound with desired biological property of the instant claims. Applicants argue that Still et al decoding without isolating the solid support. This is not persuasive, since the teachings of Still et al 'positive beads with fluorescent tag (refers to the instant tag) from among the other beads, refers to decoding to identify the compound,wherein said decoding step comprises in-situ optical interrogation of the tag, of the instant claims. Applicants' arguments seem to be emphasizing that applicants decoding refers to identifying the structure of the compound, not identifying the positive compound attached to the bead from among other beads. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., decoding the code to determine the structure of the compound) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants further argue that Still et al teaches away from the feature of the claimed invention, wherein the decoding takes place without detaching any of the tag from the solid support.

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Applicants arguments have been considered and are not persuasive, since Still et al teach after the synthesis is completed, the compounds are screened for desired property either after detachment of the ligand (compound) from the bead or while still attached, which clearly anticipates the claimed invention. The new claims 160-166, and 168-174 have been included in this rejection because the rejections of record teach all the limitations.

16. Applicant's arguments filed on 10/15/02, regarding the rejection of claims over Dower et al and US Patent 5,782,529 (Metzker) have been fully considered but they are not persuasive.

Claims 129-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dower (WO 93/06121) in view of Metzker et al (US patent 5,728,529).

Dower et al have been discussed supra.

The claimed invention differs from the prior art teachings by reciting that the fluorescent tags of specific chemical structures. Dower et al teach methods of synthesizing diverse collections of oligomer. Dower et al teach the use of identifier tags. Dower et al fail to teach the fluorescent tags of the specific structures of the claims 139-141. However, Metzker et al teach alternative dye-labeled RNA, DNA for DNA analysis. The reference teaches a new class of dyes which have improved spectral characteristics and improved stability. The reference teaches that because of the improved properties of these dyes, they are useful in any method of detection of DNA, and the spectral properties of the fluorophores are similar in wavelength and intensity to be used with conventional equipment known in the art. Thus, it would have been obvious to a person skilled in the art at the time the invention was made to use the fluorescent dyes taught by Metzker et al in the method of oligomer library synthesis and identification of the compounds of interest using identifier tags taught by Dower et al, because Metzker et al teach novel class of fluorescent dyes which can be useful to label the DNA, RNA, and has improved spectral properties, and can be used in any assay method, and Dower

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et al teach a method of using identifier tags (fluorescent or oligonucleotide) to label the solid supports to which an oligomer of a oligomer library is attached. A person skilled in the art at the time the invention was made to use the fluorescent dyes taught by Metzker et al in the method of combinatorial library of compound synthesis with the expectation of identifying the compound of interest using conventional equipment known in the art.

Applicants argue that Metzker fails to remedy the deficiencies of Dower et al, Metzker fails to teach or suggest a method of identifying compounds of interest in a library of compounds bound to solid supports wherein an optically distinguishable tag on a solid support of interest is interrogated in situ. Applicants arguments have been considered and are not persuasive, since Metzker et al teach the fluorescent dyes used in the instant claimed method, and Dower et al teach a method of synthesis and screening of a library of compounds attached to beads, and the beads are labeled with fluorescent tags. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 U. S. P. Q. 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 U. S. P. Q. 375 (Fed. Cir. 1986). From the combined teachings of Dower et al and Metzker, it would have been obvious to one skilled in the art at the time the invention was made to synthesize a combinatorial library of compounds attached to beads and identify the positive compounds still attached to the bead from among other beads. The new claims 160-166, and 168-174 have been included in this rejection because the rejections of record teach all the limitations. The rejections of record have been maintained for the reasons of record.

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No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Primary Examiner
Technology Center 1600
Art Unit 1639
01 October 2003


PADMASHRI PONNALURI
PRIMARY EXAMINER